REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the following remarks. Claims 2-20, 27-43, 46-49, 52-55 and 58-61 are pending in the application, with claims 7-20, 33, 34, 38-43, 46-49, 52-55 and 58-61 standing withdrawn from consideration by the Examiner as allegedly being drawn to non-elected subject matter. By the above amendment, withdrawn claims 7-20, 33-34, 38-43, 46-49, 52-55 and 58-61 have been canceled. Accordingly, claims 2-6, 27-32 and 35-37 remain under substantive examination.

Information Disclosure Statement

As an initial matter, Applicants respectfully request that the Examiner provide an initialed copy of the submitted PTO-1449 form listing PCT Publication No. WO95/06122. By way of background, in an IDS filed by Applicants on August 24, 2001, WO95/06122 was submitted in German. In the Examiner's Office Action mailed February 11, 2002, the Examiner stated with respect to this reference that "The AG reference in the information disclosure statement filed 8/24/01 has not been considered because it is not in English." (Action, page 2). In Applicants' Response filed May 13, 2002, this reference was supplied in English, along with a PTO-1449 listing same. In the Office Action mailed July 26, 2002 (paper No. 27), the Examiner stated that "Applicant's submission of the PCT application in English of WO95/06211 (AG reference in the IDS filed 3-29-99) is acknowledged and the signed accompanying 1449 form is attached." However, the form was not attached. Accordingly, Applicants request that the Examiner provide acknowledgement of the reference by providing a signed copy of the PTO-1449 form which has been enclosed for the Examiner's convenience.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 2-6, 27-32 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way so as to enable one skilled in the art to make and/or use the claimed invention. The specific grounds for the Examiner's rejection are addressed individually below.

1. The Examiner first asserts that the claims do not limit the cell adhesion modulating agent to an amino acid sequence between 1-50 consecutive amino acid residues

comprising SEQ ID NO: 1, but rather to any amino acid sequence between 1-50 consecutive amino acid residues of any claudin CAR sequence. The Examiner further states that the claims read on agents that do not contain SEQ ID NO: 1.

Applicants are somewhat confused by this aspect of the Examiner's rejection. The claimed invention is drawn quite specifically to a modulating agent that comprises at least five consecutive amino acid residues of a claudin CAR sequence, said claudin CAR sequence being present in a naturally occurring claudin and having the formula Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1). In this regard, the Examiner is correct that not every modulating agent encompassed by the claims will comprise the entirety of SEQ ID NO: 1. However, the modulating agents of the claimed invention do clearly require the presence of at least five consecutive amino acid residues of a naturally occurring claudin CAR sequence having the formula set forth in SEQ ID NO: 1. This claim language is submitted to be clear and well enabled by the specification as filed, and would be recognized as such by an artisan of ordinary skill. Applicants respectfully request withdrawal of this rejection, or, in the alternative, request that the Examiner offer additional clarification as to the specific basis for this rejection.

2. The Examiner also asserts with respect to claims 27 and 35-37 that it is unclear whether the claimed compositions would function as pharmaceutical compositions. According to the Examiner, Applicants specification lacks working examples providing evidence that is reasonably predictive that the claimed pharmaceutical compositions are effective for *in vivo* use. The Examiner concludes that it would require undue experimentation to practice the claimed pharmaceutical compositions with a reasonable expectation of success.

Applicants respectfully disagree that *in vivo* efficacy is required in order to enable a skilled individual to make and use a composition as claimed, *i.e.*, a composition comprising a claudin CAR sequence and a pharmaceutically acceptable carrier. All that is required is that the specification provide disclosure of how one can combine the elements of the claim, that is, a modulating agent and a pharmaceutically acceptable carrier. Such disclosure is indeed provided by the specification and, furthermore, is well known in the art.

Applicants further submit that the underlying basis of this rejection appears to be that the specification does not enable the use of the claimed pharmaceutical compositions due to

a lack of evidence demonstrating its usefulness *in vivo*. If this is true, the Examiner is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (Although the Examiner rejected pharmaceutical compositions based on § 112, a § 101 rejection for lack of utility would also have been proper.) Applicants submit that to the extent this rejection is based upon a lack of evidence demonstrating therapeutic effectiveness in humans, the rejection is inappropriate, as a demonstration of therapeutic efficacy is not required to obtain a patent. Applicants note that the Patent Office has explicitly adopted the position established by the courts that an Applicant does not have to provide actual evidence of success in treating humans where such utility is asserted. M.P.E.P. § 2107.03(I). In addition, the M.P.E.P. enunciates the Patent Office's standard for establishing therapeutic utility when stating that "if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." M.P.E.P. § 2107.03(III).

Here, the situation is analogous. Applicants have demonstrated claudin CAR modulating agents and the *in vitro* activity of same. Whether the claimed modulating agents will eventually have commercial value in the treatment of humans is not a relevant inquiry to determine patentability. Although the Action asserts that the instant application fails to provide working examples demonstrating *in vivo* efficacy, Applicants submit that such a demonstration is not necessary to establish enablement for the claimed pharmaceutical compositions. The first paragraph of § 112 requires nothing more than objective enablement, which Applicants have provided. Thus, the examples included in the present application should be considered as supportive of enablement, not a detriment, as apparently argued by the Examiner.

Despite the above, even assuming for the sake of argument that a reasonable expectation of *in vivo* efficacy was indeed considered a prerequisite to establishing enablement of a claim to a pharmaceutical composition, Applicants further submit that this reasonable expectation has been satisfied by the subject disclosure, particularly when the disclosure is coupled with what is already well known in the art of cell adhesion molecules. The artisan of

ordinary skill in this art is well aware that CAR sequences from different classes of cell adhesion molecules have been identified and that, as in the instant case, conserved core sequences of such CARs have been defined and characterized (see, *e.g.*, WO01/77146, wherein a minimal N-cadherin CAR sequence is identified and its modulating activity characterized). The skilled artisan is also aware that modulating agents based upon these CAR sequences are known to be effective for modulating cell adhesion both *in vitro* and *in vivo* (see, *e.g.*, Example 9 of WO01/77146, wherein a peptide comprising the N-cadherin CAR sequence, HAV, is demonstrated to possess modulating activity in an *in vivo* tumor model). Thus, in light of Applicants' disclosure, and further in view of what is well known in the art to which this invention pertains, the claimed invention could indeed be practiced in an *in vivo* setting without undue experimentation and with a reasonable expectation of success.

3. The Examiner further asserts that the claimed invention is not enabled due to the fact that the terms "comprises" and "having" allow for additional unrecited amino acid residues at the N- or C- termini, or both, of a claimed CAR sequence of of SEQ ID NO: 1.

Applicants agree that the claimed invention allows for additional unrecited residues at the N- and C- termini, or both, however Applicants strongly disagree that the instant claims lack enablement as a result. Open claim language as such is submitted to be entirely appropriate and allowable in the chemical and biotechnology arts, particularly where a core structural element has been defined and claimed, and where it is the presence of this core structural element, and not those residues flanking the core sequence, that are understood to be important for activity of the claimed compositions. In the instant disclosure, Applicants have indeed defined important minimal core structural elements present within claudin cell adhesion molecules that contribute to modulating activity according to the invention. The skilled artisan would understand that this modulating activity, while relying upon the presence of a CAR sequence set forth in SEQ ID NO: 1, is certainly not restricted to sequences consisting of a CAR sequence set forth in SEQ ID NO: 1. Rather, the skilled artisan would expect that additional residues may be added at the N- and/or C-termini of such a CAR sequence while not adversely effecting modulating activity. Applicants submit that the mere fact that there are a large number of possible ways in which amino acids may be present on the N- and/or C-termini of a sequence

set forth in SEQ ID NO: 1 does not preclude enablement when the skilled artisan would understand and reasonably expect that modulating agents comprising the claimed claudin CAR sequence would retain the desired modulating activity.

Moreover, to accept the position taken by the Examiner, *i.e.*, that Applicants must restrict the claimed invention to closed (*i.e.*, "consisting of") claim language belies Applicants' contribution to the art. "To provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found work or to material which meet the guidelines specified for 'preferred' materials...would not serve the constitutional purpose of promoting progress in the useful arts." (*In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976). It would be a trivial matter for a potential competitor to exploit Applicants' invention by adding one or more amino acid residues to the N- or C-termini of a claudin CAR sequence set forth in SEQ ID NO: 1, or both, to achieve an effective cell adhesion modulating agent, all the while practicing outside the literal scope of the invention to which the Examiner asserts Applicants are entitled. Applicants submit that it is improper to require closed claim language in this instance when the skilled artisan would appreciate that an entire class of modulating agents comprising SEQ ID NO: 1, which could be made and used by routine techniques disclosed in the instant specification, would indeed possess modulating activity according to the present invention.

4. Finally, the Examiner has apparently misunderstood the points Applicants attempted to establish in the previous Response filed March 11, 2003 In that Response, Applicants pointed to numerous naturally occurring claudin sequences known in the art which contain a claudin CAR sequence set forth in SEQ ID NO:1 and which could be used in practicing the claimed invention. The Examiner now states, however, that none of the illustrated naturally occurring claudin CAR sequence of SEQ ID NO: 1 has been shown to modulate cell adhesion and all of the claudin CAR sequences disclosed in the search comprises more than 50 amino acids in length.

Applicants were not attempting to take the position that the numerous naturally occurring claudin full length sequences available in the art and discussed in the Response represent modulating agents comprising no more than 50 amino acids in length, because they

clearly do not. Rather, these search results were provided by Applicants to evidence the ease with which the skilled artisan can identify naturally occurring claudin sequences as claimed and, using Applicants' disclosure as a guide, locate CAR sequences meeting the consensus sequence of SEQ ID NO: 1 and make and use such sequence with a reasonable expectation of success. Applicants are certainly not required to experimentally demonstrate that every possible claudin CAR sequence contained within a naturally occurring claudin sequence is effective for modulating cell adhesion, particularly when there would be a reasonable expectation that such modulating activity would be achieved. This reasonable expectation is submitted to be well founded both in Applicants' discovery and definition of the claudin CAR consensus sequence set forth in SEQ ID NO: 1, and further founded on the skilled artisan's understanding and expectation that once the an important core structural CAR sequence within a cell adhesion molecule has been identified and demonstrated to be effective for modulating cell adhesion, the same conserved CAR sequence from other naturally occurring claudin molecules would be expected to possess the same or similar cell adhesion modulating activity.

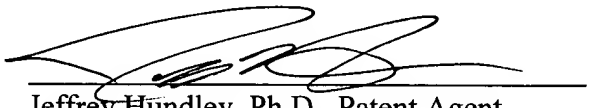
Reconsideration of the Examiner's rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration is respectfully requested.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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